Article:
Natalie, B., Michael, S. and Meena, B. (2022) Further evidence for attenuated phenotype with variants in the BMPER gene causing DSD : case report and literature review. European Journal of Medical Genetics, 65 (4). 104470. ISSN: 1769-7212

https://doi.org/10.1016/j.ejmg.2022.104470

Further evidence for attenuated phenotype with variants in the *BMPER* gene causing DSD: Case report and literature review

Batey Natalie [1], Spiller Michael [2], Balasubramanian Meena [3,4]

1 Neonatal Intensive Care Unit, Jessop Wing, Tree Root Walk, Sheffield ‡

2 Sheffield Diagnostic Genetics Service, Sheffield Children's NHS Foundation Trust

3 Sheffield Clinical Genetics Service, Sheffield Children's NHS Foundation Trust

4 Academic Unit of Child Health, Department of Oncology and Metabolism, University of Sheffield

Corresponding Author:

Balasubramanian Meena

meena.balasubramanian@nhs.net

Sheffield Clinical Genetics Service, Sheffield Children's NHS Foundation Trust, Clarkson Street, Broomhall, Sheffield, S10 2TH

0114 271 1900

Footnotes

‡ Batey Natalie current institution address: Nottingham Neonatal Service, Neonatal Intensive Care Unit, Nottingham City Hospital, Nottingham University Hospitals NHS Trust

Abstract

Diaphanospondylodysotosis and ischiospinal dysostosis are rare skeletal dysplasias with variants in the bone morphogenetic protein-binding endothelial regulator (*BMPER*). There is a continuum of clinical presentation, with DSD at the severe end of the spectrum whilst ISD is towards the milder end. Both are caused due to pathogenic variants in *BMPER*. Previous studies have reported 20 patients from 13 families. Common features in the cohort reported so far are spinal and rib anomalies but other findings illustrate phenotypic variation. Survival ranges from death within the neonatal period to alive and well at 19 years. We present three siblings with variable phenotype, adding to the evidence for a single definition of *BMPER*-related skeletal dysplasia. We highlight the need for ongoing care planning and guarded prognostication, with regular review by clinical teams.

Keywords:

Phenotype; Genetic Association Studies; Genomic Structural Variation; Bone Diseases, Developmental; Advanced Care Planning

Introduction

Skeletal dysplasias are a diverse group of heritable conditions affecting the bone and cartilage with different molecular pathways and clinical presentations. These conditions frequently present in the perinatal period; either through prenatal testing in known families, from antenatal ultrasound scan appearance or postnatal presentation. Recent technological advances, in particular genome sequencing has allowed greater understanding of the genetic and molecular basis of these conditions (Mortier, et al., 2019).

Diaphanospondylodysotosis (DSD) and ischiospinal dysostosis (ISD) are a rare dysostoses characterised predominantly by vertebral involvement, with identified variants in the bone morphogenetic protein-binding endothelial regulator (*BMPER*) (Mortier et al., 2019) (McKusick et al., 2019). Until recent advances demonstrated the genetic aetiology, both DSD and ISD were thought to be distinct conditions.

Pathogenic variants within one gene can lead to attenuated phenotypes. This has previously been described in *BMPER,* with a spectrum including both DSD and ISD (Kuchinskaya et al., 2016; Legare et al., 2017; Zong et al., 2015). Case reports have shown variants in *BMPER* with homozygous, and compound heterozygous form in the proband for both DSD and ISD (Kuchinskaya et al., 2016).

DSD is characterised by abnormal vertebral segmentation and ossification, posterior rib gaps and thoracic hypoplasia. Renal dysplasias with mono or polycystic appearance and microscopic nephroblastomatosis are the most commonly associated non-axial anomaly. Children often have a classic craniofacial appearance with ocular hypertelorism, epicanthic folds, a depressed nasal bridge with a short nose and low-set ears (McKusick et al., 2019). Previous descriptions report death within the perinatal period due to respiratory failure but longer term survivors have been described (Legare et al., 2017; Zong et al., 2015; Scottoline et al., 2012).

ISD has a similar but less severe phenotype than DSD and is characterised by minor facial dysmorphism, ischial hypoplasia and vertebral anomalies including lumbosacral hypoplasia, scoliosis and segmental defects of the cervicothoracic spine (Kuchinskaya et al., 2016).

Here we report three siblings with a diagnosis of DSD, highlighting attenuated phenotypes and the importance of ongoing multi-disciplinary medical management planning.

Clinical Report

Three affected siblings were born to consanguineous (first cousins) parents of Yemeni origin. Four other siblings were unaffected. One male sibling has molecularly confirmed Stargadt's disease, identified on retinal panel testing. The others are fit and well. All children were born at term.

In the antenatal period the first child, female was noted to have a small chest with oligohydramnios. This baby was delivered at term by emergency caesarean section due to extended breech presentation and fetal distress. Skeletal survey during the neonatal period showed absence of the sacrum with absent ossification of the vertebral bodies in the lower thoracic and lumbar spine. There were abnormal ribs with multiple rib gaps and delayed bone maturation consistent with a gestational age of 32 weeks. Her head circumference at 9 months was 42.3cm (-1SD) She required oxygen through her life, this increased over time and she died at 11 months of age.

The second sibling was suspected to have skeletal dysplasia on antenatal scans with findings of; hydrocephalus, low mineralisation of the ribs and spine, renal dysplasia and pulmonary hypoplasia. Parents requested for no active resuscitation if the baby appeared to have the same diagnosis as sibling 1. A male baby was born at term with a low heart rate, resuscitation was not initiated and he died at less than one hour of age. On examination, he was noted to have a large anterior fontanelle with widespread sutures, a flattened nasal bridge, small thorax, protruding abdomen, an anteriorly placed anus and bilateral talipes. His head circumference was 32cm (-2SD) and weight 2.6kg (-2SD). Karyotype was 46, XY and DNA was stored.

In the third sibling (male), the diagnosis was suspected following similar findings on antenatal scan at 20 weeks gestation. Fetal MRI at 21 weeks gestation revealed normal cervical spine formation but no ossified vertebral bodies below this, with normal skull and limb bones. The spinal cord length appeared normal leading to the conclusion that the vertebral bodies were cartilaginous. Rib ossification appeared to be improved on ultrasound at 29 weeks gestation.

A neonatal plan was made for delivery with neonatal team presence and management depending on the appearance and likely severity at birth. Parents did not wish for aggressive resuscitation or invasive ventilation if survival looked unlikely.

He was born in good condition but transferred to the neonatal intensive care unit (NICU) for supplemental oxygen at 10 minutes of age. His birth weight was 2.9kg (-1SD) and head circumference 34.5cm (0SD). Renal ultrasound during admission revealed multiple tiny cysts bilaterally with one larger (4mm) cyst in the right kidney. Postnatal skeletal survey showed failed ossification of the vertebral bodies, but the spine relatively stable and protected by cartilage (figure 1). He had an acceptable oximetry trace in air and was discharged home breast feeding on day 3 of life, with home oxygen to be used if symptomatic and a limitation of treatment agreement in place. Referrals were made to the paediatric respiratory and palliative care teams. This baby and both parents were reviewed in the neonatal unit by the Genetics team and trio whole genome sequencing undertaken by recruitment to the 100,000 genomes project.

At one month of age, he was discharged by the respiratory team as there had been no requirement for home oxygen. He continued to see the paediatric palliative care team with regular reviews of his limitation of care plan, an advanced care plan with family wishes was drawn up and reviewed. At 13 months of age, he was referred back to the respiratory team, the home oxygen although not required remained in situ at home. Further referrals were made to orthopaedics at 23 months and paediatric neurology at 25 months. There were no orthopaedic or neurological interventions required. At 28 months, his fine motor and social development was within normal limits but there was significant gross motor delay. He was unable to sit unsupported, due to

significant difficulties with head control. He was able to roll and use his legs to push himself around the room. At this point his weight was 7kg (>-3SD), length 70cm (>-3SD) and head circumference 49cm (0SD). Following his neurology review, he was referred to neurodisability to oversee his MDT input. Prior to this point there had been occupational therapy support for sitting aids. He is currently 3 years old, has not had any hospital admissions, never needed to use home oxygen and has had two courses of oral antibiotics for lower respiratory tract infections.

Methods

Trio whole Genome Sequencing for the 100,000 Genomes Project was performed by Illumina. Bioinformatic analysis was performed by Genomics England (GeL) using bcftools v1.2 and platypus v0.8.1. Any single-nucleotide variant or indel < 50bp meeting the following criteria was analysed for clinical significance using ACMG/ACGS criteria (Richards et al., 2015; Ellard et al., 2020): (1) ExAc population frequency < 2%, (2) consistent with the mode of inheritance for the gene (*de novo* for autosomal dominant genes, biallelic for autosomal recessive, monoallelic for X-linked or imprinted) (3) within coding sequence or 8 nucleotides up- or down-stream, (4) in a gene on the Genomics England PanelApp virtual panels Intellectual disability (2.508) and Skeletal dysplasia (1.126). The average coverage for both panels was 27x. Clinically significant variants were confirmed by Sanger Sequencing.

Copy Number Variants were called using Canvas (v1.3.1). CNVs were analysed for clinical significance if they met the following criteria: (1) size at least 10kb (2) in a gene on the Genomics England PanelApp virtual panels Intellectual disability (2.508) and Skeletal dysplasia (1.126).

Results

Three single nucleotide variants were analysed for clinical significance. Variants in in *IARS1* and *DDX3X* were assessed as being unlikely to be clinically significant.

The third variant was a homozygous missense variant in *BMPER,* c.1108C>T p.(Pro370Ser) (using transcript NM_133468.4). This variant is absent from control populations (gnomAD v2.1.1 and v3), and affects the same amino acid as a previously reported pathogenic variant (Funari et al., 2010). This nucleotide is highly conserved (phyloP: 6.26) and individual *in silico* predictive tools predicted this variant to be pathogenic (PolyPhen-2 HumVar 1.000; SIFT 0.000, PROVEAN -7.47) but the prediction of meta-predictor REVEL was inconclusive (0.508). Genomics England data, confirmed by Sanger sequencing, showed that the variant was inherited biparentally. MDT discussion concluded that the proband's phenotype is a highly specific match to *BMPER* gene-disease association.

On the basis of this evidence, the *BMPER* c.1108C>T p.(Pro370Ser) variant was classified as likely pathogenic using ACMG/ACGS criteria PM2, PM5, PM3_supporting, PP4_moderate.

Discussion

We report three affected siblings born to a consanguineous couple. DSD and ISD are rare diagnoses with few reports in the literature. However, there is increasing evidence in the literature to support a *BMPER*-related skeletal dysplasia with overlapping phenotypes and variable expression (Kuchinskaya et al., 2016; Salian et al., 2018; Legare et al., 2017; Zong et al., 2015). We provide further evidence to the discussion by Greenbaum et al. (2019) that DSD and ISD should be described as *BMPER*-related skeletal dysplasia due to the attenuated phenotype within our siblings all born at term.

Previous case series have described families with multiple affected children (Greenbaum et al., 2019; Zong et al., 2015; Ben-Neriah et al., 2011). Zong et al. (2015) described a series of four siblings with similar phenotype. Further phenotypic data is not available on the series by Greenbaum et al. (2019) and Ben-Neriah et al. (2011) due to early termination of pregnancy.

We have identified 20 patients with *BMPER* variation leading to a diagnosis of DSD or ISD in the literature, or untested siblings with a positive family history of *BMPER* pathogenic variants and similar antenatal findings. Table 1 shows the gene variants in *BMPER* previously reported and

from our study, 23 individuals from 14 families. The patients are either genetically confirmed or phenotypically similar siblings of probands with confirmed variants. In the case presented by Legare et al. (2017), the child was initially diagnosed with ISD but later reclassified to DSD. Six families have compound heterozygous variants and seven homozygous variants. In the other, the second variant was not identified, the authors postulate an intronic variant or a variant resulting in a deletion on the other allele, unmasking a recessive variant (Funari et al., 2010). Table 1 demonstrates the range in location for the variants, the only recurrent *BMPER* variant previously identified was in the two families presented in one report (Ben-Neriah et al., 2011). Biallelic variants have been found in both ISD and DSD and variants reported include both missense and nonsense. From the available literature there appears to be no correlation between variant and phenotype severity, however this is limited by the low number of reported patients.

Clinical information was available for patients with 17 of the previously reported 20 *BMPER* variants, this is summarised in Table 2. There was Termination of pregnancy in 6 patients (Greenbaum et al., 2019; Hofstaetter et al., 2018; Ben-Neriah et al., 2011) and one stillbirth, felt to be secondary to an umbilical cord accident (Zong et al., 2015). Of the 10 liveborn babies, 1 died at 4 months (Ben-Neriah et al., 2011) one at 15 months (Ben-Neriah et al., 2011), and another at 4 years (Tasian et al., 2012; Funari et al., 2010; Scottoline et al., 2012) the remainder were alive at the time of report with the oldest aged 19 years (Kuchinskaya et al., 2016). There are other reports of DSD and ISD in the literature but genetic results are not reported (Kaissi et al., 2007; Spranger et al., 2001; Nishimura et al., 1999; Nishimura et al., 2003; Amasri et al., 2017; Vatanavicharn et al., 2007)

Table 2, demonstrates common phenotypes between all reported individuals. Liveborn children had rib and spinal anomalies, with all having reduced or absent vertebral ossification. The baby stillborn at term also had reduced vertebral ossification and rib numbers. Other common features included: reduced rib number, renal and pelvic anomalies, a short trunk and facial dysmorphism.

The most common renal anomaly was hydronephrosis but there are reports of nephroblastomatosis, with one child developing a Wilm's tumour (Tasian et al., 2012) and evidence on post-mortem in another (Zong et al., 2015). Of interest, 40% of patients were described to have developmental delay, this included not only motor delay as would be expected but also delay in speech. Common antenatal findings not only included spinal anomalies but an increased nuchal translucency on early scan.

There are previously reported overlapping phenotypes with one child being reclassified from ISD to DSD based on the severity of radiological imaging (Legare et al, 2017) and renal anomalies reported in both ISD and DSD (Kuchinskaya et al, 2016). Although limited by early termination of pregnancy two fetuses in the siblings reported by Greenbaum et al. (2019) did not have the typical renal findings previously reported in DSD. This information combined with our family suggests a continuum between ISD and DSD.

There is often a presumption of lethality due to previous family history. However, of the liveborn children previously reported, 70% were alive at the time of report, ranging from 2-19 years of age. In the family reported here, we have shown variable phenotypes with the same gene variant. For these reasons, it is important to discuss variable expressivity and be guarded around prognosis when discussing the diagnosis with families, either in the antenatal or postnatal period. There should be long term parallel planning from the prenatal period onwards and counselling geared both towards early death, but also consideration of the potential for longer term survival. Clear management plans should be made at each transition point. For example, a pre-birth plan outlining the management during labour, birth and the neonatal period. If the baby survives birth and the immediate neonatal period, a plan for discharge home and follow-up responsibilities should be made, along with a transition from neonatal to paediatric services. As the prognosis can be uncertain, follow-up should include both regular reviews of any advanced care directives and palliative care requirements but also a review of the clinical status and any potential ongoing care needs.

Long term medical complications described in patients with DSD include restrictive pulmonary disease, hyperopia, hearing loss, neurogenic bowel and bladder and musculoskeletal problems secondary to the spinal anomalies (Legare et al., 2017). For this reason, it seems prudent to ensure follow-up with paediatric respiratory and neurodisability teams is in place.

There may be more commonality between phenotypes than we describe. Our analysis is limited by the data reported. Antenatal or postnatal negative findings are not reported in all papers.

This report adds to the evidence of a spectrum of overlapping phenotypes in *BMPER* variants and we recommend a redefinition of ISD and DSD to BMPER-related skeletal dysplasia. For children and families with this diagnosis, there needs to be consideration of care planning from the antenatal period with regular ongoing review.

CRediT author statement: Batey Natalie: writing – original draft preparation, investigation, visualisation. Spiller Michael – resources, validation. Balasubramanian Meena: conceptualisation, writing – review and editing, supervision.

Acknowledgments: We thank the family for consenting to this publication.

Conflicts of Interest: The authors have no conflicts of interests to declare.

Funding: No funding has been received by any authors.

Data Sharing: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Table 1: Gene variants found in *BMPER*

Affected family members (n)	DNA	Protein	Consanguinity	Zygosity	Reference	Diagnosis
3	c.1108C>T	p.Pro370Ser	Y	Homozygous	Our study	
3	c.410T>A	p.Val137Asp	N	Homozygous	(Greenbaum, 2019)	DSD
1	c.416C>G c.924G>A	p.Thr139Arg p.Trp314*	N	Compound heterozygous	(Kushinskaya, 2016)	ISD
1	c.1672C>T c.1988G>A c.1672C>T	p.Arg588* p.Cys662Tyr p.Arg588*	N	Compound heterozygous	(Kushinskaya, 2016)	ISD
3	C.310C>T	p.Gln104*	Y	Homozygous	(Ben-Neriah, 2011)	DSD
1	c.310C>T	p.Gln104*	N	Homozygous	(Ben-Neriah, 2011)	DSD
1	c.496T>A;501_502delGT	p.Cys166Ser;Phe168*	N	Homozygous	(Hofstaetter, 2018)	DSD
4	c.251G>T c.1078+5G>A	p.Cys84Phe	N	Compound heterozygous	(Zong, 2015)	DSD
1	7p14.3p14.2 deletion c.322T>C	p.C108R	N	Heterozygous	(Legare, 2017)	ISD/DSD
1	c.314G>A	p.Cys105Tyr	Y	Homozygous	(Salian, 2018)	ISD
1	c.925C>T	p.Gln309*	Unknown	Homozygous	(Funari, 2010)	DSD
1	c.26_35del10ins14 c.1032+5G>A	p.Ala9Glufs*4	Unknown	Compound heterozygous	(Funari, 2010)	DSD
1	c.514C>T	p.Gln172*	Unknown	Heterozygous †	(Funari, 2010)	DSD
1	c.1109C>T c.1638T>A	p.Pro370Leu p.Cys546*	Unknown	Compound heterozygous	(Funari, 2010)	DSD

†second mutation not identified, suggesting other allele results in deletion or does not reside in coding region

Table 2: Clinical features of BMPER variants in literature to date

	Reported finding (%)	Reference
ANTENATAL		
Increased nuchal translucency	35%	(Ben-Neriah, 2011; Greenbaum, 2019; Hofstaetter, 2018)
Spinal anomalies	53%	(Hofstaetter, 2018; Greenbaum, 2019; Legare, 2017; Ben-Neriah, 2011; Zong, 2015)
Absent vertebrae	29%	(Ben-Neriah, et al., 2011; Hofstaetter, Courage, Bartholdi, Biskup, & Raio, 2018)
Dysplastic vertebrae	6%	(Ben-Neriah, 2011)
Rib anomalies	24%	(Ben-Neriah, 2011; Greenbaum , 2019; Hofstaetter, 2018)
Thoracic shape anomalies	12%	(Ben-Neriah, 2011; Greenbaum, 2019)
Renal	24%	(Ben-Neriah, 2011; Greenbaum, 2019)
Echogenic kidneys	18%	(Ben-Neriah, 2011; Greenbaum, 2019)
Renal cysts	12%	(Ben-Neriah, 2011; Greenbaum, 2019)
Absence/abnormality of nasal bone	12%	(Greenbaum, 2019; Hofstaetter, 2018)
Reduced ossification of skull	6%	(Greenbaum, 2019)
POSTNATAL		
Respiratory distress at birth	30%	(Ben-Neriah, 2011; Kuchinskaya, 2016; Scottoline, 2012)
Thoracic hypoplasia	40%	(Kuchinskaya, 2016; Legare, 2017; Ben-Neriah, 2011; Scottoline, 2012)
Facial dysmorphism	60%	(Salian, 2018; Kuchinskaya, 2016; Legare, 2017; Ben-Neriah, 2011; Scottoline, 2012)
Enlarged fontanelles	10%	(Ben-Neriah, 2011)
Short neck	50%	(Salian, 2018; Legare, 2017; Ben-Neriah, 2011; Scottoline, 2012)
Short trunk	70%	(Salian, 2018; Kuchinskaya, 2016; Legare, 2017; Ben-Neriah, 2011; Scottoline, 2012)
Spinal anomalies	100%	(Salian, 2018; Kuchinskaya, 2016; Legare, 2017; Ben-Neriah, 2011; Zong, 2015; Scottoline, 2012)
Kyphosis	40%	(Salian, 2018; Legare, 2017; Ben-Neriah, 2011; Zong, 2015)
Scoliosis	50%	(Kuchinskaya, 2016; Ben-Neriah, 2011; Zong, 2015)
Reduced/ABSENT ossification	100%	(Legare, 2017; Kuchinskaya, 2016; Ben-Neriah, 2011; Zong, 2015; Scottoline, 2012)
Vertebral hypoplasia	40%	(Kuchinskaya, 2016; Legare, 2017; Zong, 2015)
Rib anomalies	100%	(Salian, 2018; Kuchinskaya, 2016; Legare, 2017; Ben-Neriah, 2011; Zong, 2015; Scottoline, 2012)
Reduced number	70%	(Kuchinskaya, 2016; Legare, 2017; Ben-Neriah, 2011; Zong, 2015; Scottoline, 2012)
Rib gaps	10%	(Legare, 2017)
Dysplastic	40%	(Salian, 2018; Kuchinskaya, 2016; Legare, 2017)
Renal anomalies	50%	(Salian, 2018; Legare, 2017; Kuchinskaya, 2016; Ben-Neriah, 2011; Scottoline, 2012)
Hydronephrosis	30%	(Salian, 2018; Legare, 2017; Kuchinskaya, 2016)
Cysts	20%	(Ben-Neriah, 2011; Scottoline, 2012)
Nephroblastomatosis	10%	(Scottoline, 2012)
Pelvic anomalies	50%	(Salian, 2018; Kuchinskaya, 2016; Legare, 2017; Scottoline, 2012)
Protruding abdomen	40%	(Kuchinskaya, 2016; Ben-Neriah, 2011; Scottoline, 2012)
Chronic otitis media	40%	(Legare, 2017; Zong, 2015)
Developmental delay	40%	(Salian, 2018; Scottoline, 2012; Kuchinskaya, 2016)

Figure 1: chest and abdominal x-ray demonstrating failed ossification of the vertebral bodies

References

Amasri, M., Kishta, W., Abduljabbar , F. H., Alrlet, V., Saran , N., & Oullet, J. (2017). Ischiospinal Dysostosis in a Child with Pierre-Robin Syndrome. *Case Reports in Orthopaedics*. doi:10.1155/2017/8263536

Ben-Neriah, Z., Michaelson-Cohen , R., Inbar-Feigenberg, M., Nadjari, M., Zeligson, S., Shaag, A., . . . Levy-Lahad, E. (2011). A Deleterious Founder Mutation in the BMPER Gene Causes Diaphanospondylodysostosis (DSD). *American Journal of Medical Genetics Part A, 155*, 2801-2806. doi:10.1002/ajmg.a.34240

Ellard, S., Baple, E. L., Callaway, A., Berry, I., Forrester, N., Turnball, C., . . . McMullan, D. J. (2020, February 4). *ACGS Best Practice Guidelines for Variant Classification in Rare Disease 2020.* Retrieved from Association for Clinical Genomic Science: http://www.acgs.uk.com/quality/best-practice-guidelines

Funari , V. A., Krakow, D., Nevarez, L., Chen, Z., Funari, T. L., Vatanavicharn, N., . . . Cohn, D. H. (2010). BMPER Mutation in Diaphanospondylodysostosis Identified by Ancestral Autozygosity Mapping and Targeted High-Throughput Sequencing. *The American Journal of Human Genetics, 87*, 532-537. doi:10.1016/j.ajhg.2010.08.015

Greenbaum , L., Gilboa, Y., Raas-Rothschild, A., Barel, O., Kol, N., Reznik-Wolf, H., . . . Berkenstadt, M. (2019). Diaphanospondylodysostosis: Refining the prenatal diagnosis of a rare skeletal disorder. *European Journal of Medical Genetics, 62*, 167-171. doi:10.1016/j.ejmg.2018.07.004

Hofstaetter, C., Courage, C., Bartholdi, D., Biskup, S., & Raio, L. (2018). Prenatal diagnosis of diaphanospondylodysostosis (DSD): a case report. *Clincial Case Reports, 6*(2), 420-425. doi:10.1002/ccr3.1368

Kaissi, A. A., Chehida, F. B., Latos-Bielenska, A., Gharbi, H., Ghachem, M. B., Hendaoui, L., & Kozlowski, K. (2007). A Novel Form of Ischio-vertebral syndrome. *Skeletal Radiology, 36*, 77-81. doi:10.1007/s00256-005-0073-1

Kuchinskaya, E., Grigelioniene, G., Hammarsjö, A., Lee, A. R., Högberg, L., Grigelionis, G., . . . Cho, T. J. (2016). Extending the phenotype of BMPER-related skeletal dysplasia to ischiospinal dysostosis. *Orphanet Journal of Rare Diseases, 11*, 1. doi:10.1186/s13023-015-0380-0

Legare, J. M., Seaborg, K., Laffin, J., & Giampietro, P. F. (2017). Diaphanospondylodysostosis and ischiospinal dysotosis, evidence for one disorder with variable expression in a patient who has survived to age 9 years. *Am J Med Genet, 173A*, 2808-2813. doi:10.1002/ajmg.a.38395

McKusick, V. A., Przylepa, K. A., O'Neill, M. J., & Hanson, K. R. (2019, November 25). *OMIM*. Retrieved August 13, 2020, from https://omim.org/entry/608022

Mortier, G. R., Cohn, D. H., Cormier-Daire, V., Hall, C., Krakow, D., Mundlos, S., . . . Warman, M. L. (2019). Nosology and Classification of genetic skeletal disorders:2019 revision. *Am J Med Genet, 179A*, 2393-2419. doi:10.1002/ajmg.a.61366

Nishimura, G., Kim, O. H., Sato, S., & Hasegawa, T. (2003). Ischiospinal dysostosis with Cystic Kidney Disease: report of two cases. *Clinical Dysmorphology, 12*, 101-104. doi:10.1097/00019605-200304000-00005

Nishimura, G., Kimizuka, M., Shiro, R., Nii, E., Nishiyama, M., Kawano, T., . . . Kawada, Y. (1999). Ischio-spinal dysostosis: a previously unrecognised combination of malformations. *Pediatric Radiology, 29*, 212-217. doi:10.1007/s002470050574

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., . . . ACMG Laborartory Quality Assurance Committee. (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine, 17*, 405-24. doi:10.1038/gim.2015.30

Salian, S., Nampoothiri, S., Shukla, A., & Girisha, K. M. (2018). Further evidence for causation of ischiospinal dysostosis by a pathogenic variant in BMPER and expansion of the phenotype. *Congenital Anomalies, 59*(1), 26-27. doi:10.1111/cga.12285

Scottoline B, R. S. (2011). Long-term Survival with Diaphanospondylodystosis (DSD): Survival to 5 years and Further Phenotypic Characteristics. *American Journal of Medical Genetics Part A, 158A*, 1447-1451. doi:10.1002/ajmg.a.35352

Scottoline, B., Rosenthal, S., Keisari, R., Kirpekar, R., Angell, C., & Wallerstein, R. (2012). Long-term survival with diaphanospondylodysostosis (DSD): survival to 5 years and further phenotypic characteristics. *Am J Med Genet, 158A*, 1447-1451. doi:10.1002/ajmg.a.35352

Spranger, J., Self, S., Clarkson, K. B., & Pai, G. S. (2001). Ischiospinal dysostosis with Rib Gaps and Nephroblastomatosis. *Clinical Dysmorphology, 10*, 19-23. doi:10.1097/00019605-200101000-00004

Tasian, S. K., Kim, G. E., Miniati, D. N., & DuBois, S. G. (2012). Development of Anaplastic Wilms Tumouir and Subsequent Relapse in a Child with Diaphanospondylodysostosis. *J Pediatr Hematol Oncol., 34*(7), 548-551. doi:10.1097/MPH.0b013e3182465b58

Vatanavicharn, N., Graham, J. J., Curry, C. J., Pepkowitz, S., Lachman, R. S., Rimoin, D. L., & Wilcox, W. R. (2007). Diaphanospondylodysostosis: six new cases and exclusion of the candidate genes, PAX1 and MEOX1. *Am J Med Genet A, 143A*(19), 2292-302. doi:10.1002/ajmg.a.31934

Zong, Z., Tees, S., Miyanji, F., Fauth, C., Reilly, C., Lopez, E., . . . Lehman, A. (2015). BMPER variants associated with a novel, attenuated subtype of diaphanospondylodysostosis. *Journal of Human Genetics, 60*, 743-747. doi:10.1038/jhg.2015.116